

Anesthesiology
1996; 84:64-9
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Electroencephalogram Bispectral Analysis Predicts the Depth of Midazolam-induced Sedation

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Background: The electroencephalogram (EEG) has been used to study the effects of anesthetic and analgesic drugs on central nervous system function. A prospective study was designed to evaluate the accuracy of various EEG parameters for assessing midazolam-induced sedation during regional anesthesia.

Methods: Twenty-six consenting adult patients were administered 4.5–20 mg intravenous midazolam (in increments of 0.5–1-mg bolus doses every 6–10 min) until they became unresponsive to tactile stimulation (*i.e.*, mild prodding or shaking). The EEG was continuously recorded from a bifrontal montage (FP₁-C₂ and FP₂-C₂) to obtain the bispectral index (BI), 95% spectral edge frequency (SEF), median frequency (MF), and δ , θ , α , and β power bands. Sedation was assessed clinically at 6–10-min intervals using the Observers' Assessment of Alertness/Sedation (OAA/S) scale, with 1 = no response (unconsciousness) to tactile stimulation to 5 = wide awake. The EEG parameters were correlated with the OAA/S scores using nonparametric Spearman's rank-correlation analysis. Kruskal-Wallis analysis of variance was used to determine significant changes in EEG parameters during the onset of and recovery from midazolam-induced sedation.

Results: Of the EEG parameters studied, the BI exhibited the best correlation with OAA/S scores during both the onset (Spearman's Rho = 0.815) and recovery (Spearman's Rho = 0.596) phases. With increasing sedation, there was a progressive decrease in the BI (OAA/S score of 5: BI = 95.4 ± 2.3 ; 4: 90.3 ± 4.5 ; 3: 86.6 ± 4.6 ; 2: 75.6 ± 9.7 ; 1: 69.2 ± 13.9). A similar pattern was found for the 95% SEF as the OAA/S score decreased from 4 to 1. Similarly, EEG-BI increased with recovery from the sedative effects of midazolam (OAA/S score = 2: BI = 75.2 ± 10.2 ; 3: 82.3 ± 7.3 ; 4: 90.8 ± 6). However, no consistent changes were found with the other EEG parameters. The mean EEG values between OAA/S scores 3 and 2 and between OAA/S

S scores 2 and 1 during the onset and recovery phases from midazolam-induced sedation, defined as EEG₅₀ values for response to verbal command (EEG_{50-vc}) and to shaking of the head (EEG_{50-sh}), were 79.3 ± 8 and 70.8 ± 14.3 , respectively, for EEG-BI. The EEG-BI displayed the smallest coefficients of variation for the EEG_{50-vc} and EEG_{50-sh} values.

Conclusions: The EEG-BI appears to be a useful parameter for assessing midazolam-induced sedation and can predict the likelihood of a patient responding to verbal commands or to shaking of the head during midazolam-induced sedation. (Key words: Anesthetics, intravenous: midazolam. Monitoring, brain: bispectral analysis; electroencephalogram. Sedation.)

BENZODIAZEPINES frequently are administered during local and regional anesthesia to relieve patients' anxiety, decrease intraoperative awareness, and to provide the desired level of sedation (or sleepiness). Inadvertent overdosage with benzodiazepines can result in restlessness and respiratory and/or circulatory depression and may contribute to adverse neurologic outcomes.¹ Careful monitoring of the patients' sedation level is important to avoid these complications. To facilitate the clinical evaluation of midazolam-induced sedation, Chernik *et al.* developed the Observers' Assessment of Alertness/Sedation (OAA/S) scale (Appendix).² This technique of assessment requires that the patient be stimulated at frequent intervals during the operation, a practice that can be disturbing to both the patient and the surgeon. A further limitation of the OAA/S scale is that it requires the patients' cooperation and is subject to testing fatigue. Therefore, the availability of a reliable, noninvasive sedation monitor would be highly desirable.

The electroencephalogram (EEG) has been shown to change with sleep,³ sedation,^{4–6} and general anesthesia.^{7,8} Different anesthetic and analgesic drugs alter the EEG in a drug-specific fashion.^{4,6,9–12} This makes precise interpretation of EEG changes for assessing depth of anesthesia or sedation difficult when a combination of anesthetic and analgesic drugs has been administered. To overcome the difficulties associated with conventional EEG monitoring, computerized EEG-derived parameters (*e.g.*, power bands: α , β , δ and θ),

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Received from the Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas. Submitted for publication March 3, 1995. Accepted for publication September 19, 1995. Supported in part by Aspect Medical Systems, Inc., Natick, Massachusetts, and the Ambulatory Anesthesia Research Foundation, Dallas, Texas.

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frequency variables (95% SEF and MF), and phase-coupling (bispectral index, BI) have been evaluated.

Recent studies involving the EEG-BI, a technique that quantifies interfrequency phase-coupling, suggest that this EEG index correlates best with the depth of anesthesia.¹³⁻¹⁷ However, correlation of the EEG-BI with the level of sedation during surgery has not been previously studied. Therefore, we designed this study to compare the accuracy of the EEG-BI with other commonly used EEG parameters for assessing midazolam-induced sedation during regional anesthesia.

Materials and Methods

Twenty-six (ASA physical status 1 and 2) men scheduled for elective surgery under regional anesthesia were studied according to a protocol approved by the institutional review board. Written informed consent was obtained from all the study patients. Patients with known neurologic disease, as well as significant cardiovascular, respiratory, and hepatic disease, were excluded from participating in this study.

Patients ranged in age from 22 to 70 yr (52 ± 15 yr; mean \pm SD) and in weight from 65 to 120 kg (86 ± 14 kg). All patients fasted for at least 6 h before surgery and received no preoperative medication. Routine monitors included electrocardiogram, noninvasive automatic blood pressure cuff, and a pulse oximeter. In addition, gold cup EEG electrodes (Grass Instruments, Quincy, MA) were placed on the scalp with conductive gel in the following configuration: FP₁-C_z and FP₂-C_z (International 10-20 System of electrode placement). A ground electrode was placed behind the right ear lobe, and the electrodes were secured with collodion. The impedance of each electrode was less than 5 K Ω . To minimize artifacts, patients were instructed not to open their eyes, talk, or move during the EEG recording intervals before making the OAA/S assessments. The EEG waveforms were recorded at 128 Hz using the EEG monitor (model B500, Aspect Medical Systems, Natick, MA). The quantitative EEG parameters were calculated at 4-s epochs and recorded at 15-s intervals. During the surgical procedure, all patients received supplemental oxygen *via* nasal cannula at a flow rate of 3-4 l \cdot min⁻¹.

After placement of the monitoring devices, a regional anesthetic block (*i.e.*, spinal, epidural, or axillary) was performed depending on the operative requirements. After achieving adequate surgical analgesia, 1 mg intravenous midazolam was administered. Thereafter,

midazolam was titrated in 0.5-1-mg increments at 6-10-min intervals to achieve an OAA/S sedation level of 1. The total doses of midazolam ranged from 4.5 to 20 mg, with a mean value (\pm SD) of 9.1 ± 4.3 mg. After attaining an OAA/S score of 1, no additional sedative medication was administered, and recovery from sedation was observed until the OAA/S score returned to 4. During the onset and recovery phases, sedation was assessed at 6-10-min intervals using the OAA/S scale. Assessments of sedation (OAA/S) were performed by one investigator (J.L.) to minimize interobserver variability.

The EEG parameters analyzed included the total power in the δ (<4 Hz), θ (4-8 Hz), α (8-13 Hz), and β (14-40 Hz) frequency bands; MF (*i.e.*, the frequency at which half the power was at higher frequencies and half at lower frequencies); and 95% SEF (*i.e.*, the frequency at which 95% of the total power was at lower frequencies); and the BI. A detailed description of the fundamentals of bispectral analysis has been reported in previously published studies.^{17,18} All the patients remained well oxygenated ($Sp_{O_2} > 95\%$) and normotensive (MAP > 80% of the baseline values) throughout the study period.

In this study, the BI values reported are the average of real-time bispectral indices obtained from channels 1 and 2 (FP₁-C_z and FP₂-C_z). The values of EEG parameters at each OAA/S score were calculated by averaging all the values during the 45-s interval immediately before assessment of the sedation level. Mean values and SD were calculated for all EEG parameters at each OAA/S score. The mean EEG values between OAA/S scores 3 and 2 and between OAA/S scores 2 and 1 during the onset and recovery phases from midazolam-induced sedation were defined as the EEG_{50 VC} values for response to verbal command (EEG_{50 VC}) and to shaking of the head (EEG_{50 SH}), respectively. Coefficients of variation for EEG_{50 VC} and EEG_{50 SH} were calculated by dividing the SD by the mean EEG value and multiplying by 100.

Kruskal-Wallis analysis of variance was used to determine significant changes in each EEG parameter during the onset of and recovery from sedation. The nonparametric Spearman's rank-correlation analysis was performed to evaluate the relationship between OAA/S scores and EEG-BI or 95% SEF. The EEG-BI-quantal response relationships were plotted as the EEG-BI and the percentage of patients responding to a verbal command or to shaking of their head. Differences with a *P* value <0.05 were considered statistically significant.

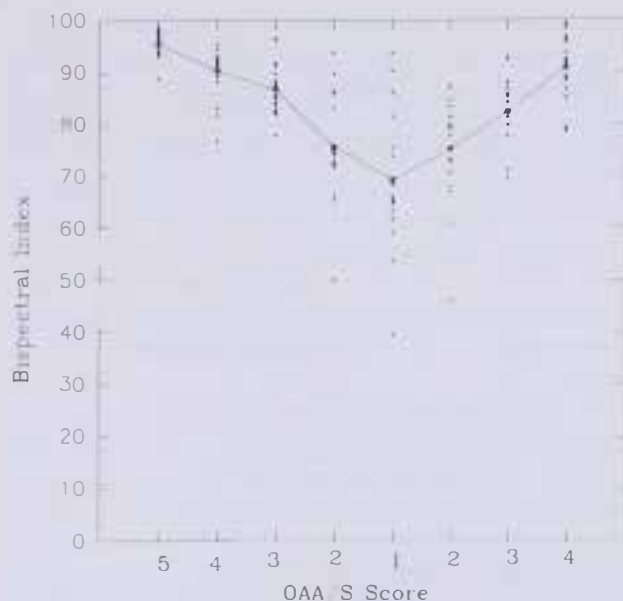


Fig. 1. Electroencephalogram bispectral index (BI) as a function of the level of midazolam-induced sedation during the onset and recovery phases. The values are either mean or individual (scatterplot).

Results

With progressively increasing sedation from an OAA/S score of 5 to 1, the EEG-BI values decreased from 95.4 ± 2.3 to 69.2 ± 13.9 (fig. 1, table 1). Similarly, the 95% SEF values decreased from 20.1 ± 4.5 to 15.7 ± 3.8 as the level of sedation progressed from an OAA/S score of 4 to 1 (fig. 2, table 1). During recovery, the EEG-BI increased from 69.2 ± 13.9 to 90.8 ± 6 as the OAA/S score increased from 1 to 4 (fig. 1, table 2). In contrast, the 95% SEF did not increase significantly as

Table 1. Spectral Edge Frequency (SEF; 95%) and Bispectral Index (BI) and Observer's Assessment of Alertness/Sedation (OAA/S) Score during the Onset Phase

OAA/S	95% SEF*	BI†
5	18.8 ± 5.3	95.4 ± 2.3
4	20.1 ± 4.5	90.3 ± 4.5
3	19.4 ± 2.7	86.6 ± 4.6
2	17.7 ± 2.6	75.6 ± 9.7
1	15.7 ± 3.8	69.2 ± 13.9

Values are either numbers or means \pm SD.

* Significant decrease in 95% SEF with change in OAA/S score from 4 to 1 ($P < 0.05$).

† Significant decrease in BI with change in OAA/S score from 5 to 1 ($P < 0.05$).

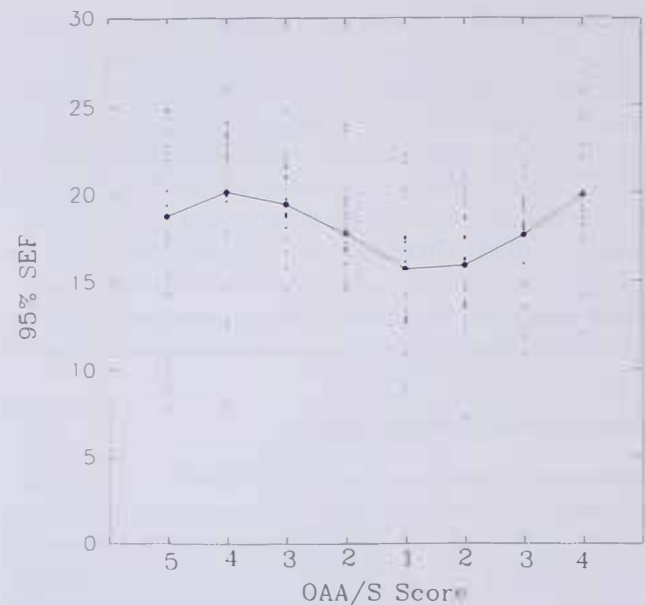


Fig. 2. Ninety-five-percent spectral edge frequency (SEF) as a function of the level of midazolam-induced sedation during the onset and recovery phases. The values are either mean or individual (scatterplot).

OAA/S level progressed from 1 to 4 (fig. 2, table 2). The EEG-BI correlated closely with the OAA/S scores during both the onset (Spearman's $Rho = 0.815$; $P < 0.0001$) and recovery (Spearman's $Rho = 0.596$; $P < 0.0001$) phases (fig. 3). The 95% SEF was closely correlated only during the onset phase of sedation as OAA/S progressed from 4 to 1 (Spearman's $Rho = 0.459$; $P < 0.0001$).

With the decrease in EEG-BI, the cumulative percentage of patients responding to verbal commands decreased. The EEG-BI versus cumulative percentage response to shaking of the patient's head followed a similar pattern but was shifted to the left of the EEG-BI responses to verbal commands (fig. 4). These data sug-

Table 2. Spectral Edge Frequency (SEF; 95%) and Bispectral Index (BI) and Observer's Assessment of Alertness/Sedation (OAA/S) Score during the Recovery Phase

OAA/S	95% SEF	BI*
1	15.7 ± 3.8	69.2 ± 13.9
2	15.9 ± 3.5	75.2 ± 10.2
3	17.6 ± 3.5	82.3 ± 7.3
4	19.9 ± 14.1	90.8 ± 6

Values are either numbers or mean \pm SD.

* Significant increase in BI with changes in OAA/S score from 1 to 4 ($P < 0.05$).

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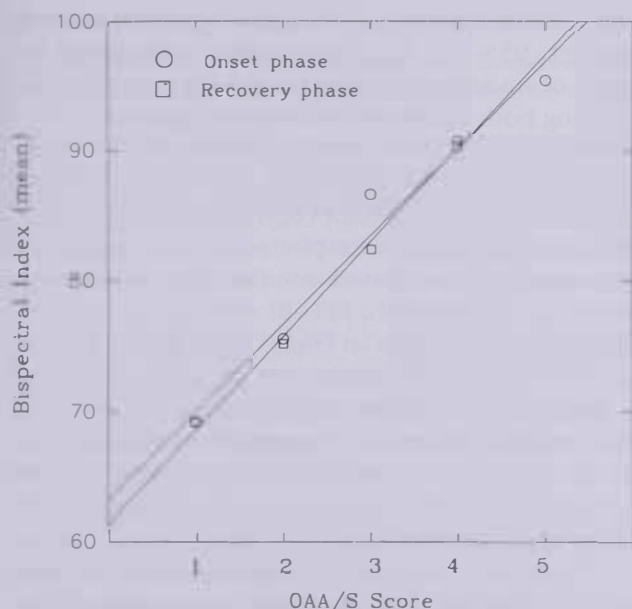


Fig. 3. Correlation of the electroencephalogram bispectral index (BI) with OAA/S score during the onset (Spearman's $Rho = 0.815$) and recovery (Spearman's $Rho = 0.596$) phases of midazolam-induced sedation.

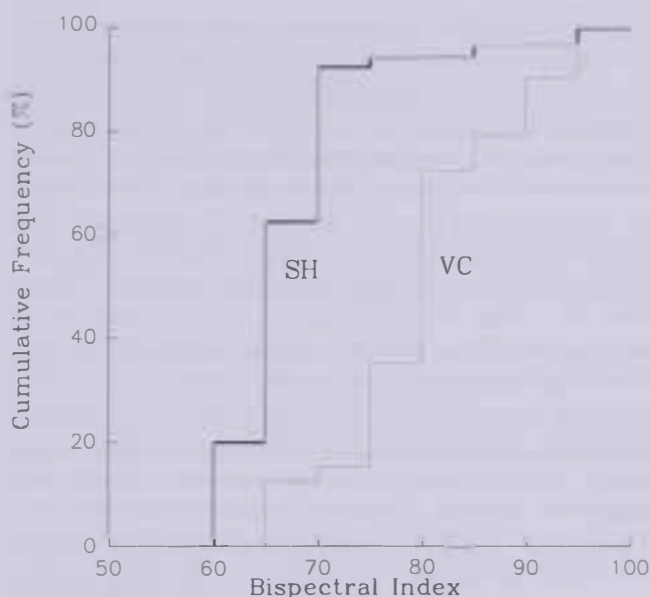


Fig. 4. Cumulative percentage of patients responding to verbal command (VC) or to shaking of the head (SH) as a function of the electroencephalogram bispectral index (BI) during midazolam-induced sedation.

gest that a greater depth of sedation (*i.e.*, lower EEG-BI values) is required to prevent a response to a physical stimulus (*i.e.*, shaking the patient) than to a verbal stimulus. The coefficients of variation of BI for EEG_{50-VC} (10.2%) and EEG_{50-SH} (19.8%) were less than with the other EEG parameters studied (table 3).

No consistent correlations were found for the δ or θ power bands or MF values and OAA/S score during the onset of or recovery from sedation. The total power in the α band increased as the OAA/S score changed from 5 to 2 (OAA/S score: α power = $5:9.8 \pm 8$; $4:14.3 \pm 11$, $3:24.2 \pm 11.7$; $2:28.3 \pm 11.8$). In contrast, β power decreased as the OAA/S score decreased from 4 to 1 (OAA/S score: β power = $4:26.1 \pm 12.5$; $3:25.4 \pm 12.6$, $2:18.1 \pm 7.6$; $1:13.2 \pm 9.9$). During the recovery phase, the α or β power did not change significantly as OAA/S score increased from 1 to 4.

Discussion

This study demonstrates that the EEG-BI correlates with midazolam-induced sedation as assessed by the OAA/S rating scale. With increases in sedation, there were predictable decreases in the EEG-BI. Similarly, 95% SEF decreased as OAA/S score decreased from 4

to 1. During the recovery phase, decreasing sedation was associated with increasing EEG-BI values. In addition, the small coefficients of variation of EEG_{50-VC} and EEG_{50-SH} for EEG-BI suggest that the EEG-BI may provide a better correlation with sedation than the other EEG parameters studied, including the 95% SEF. Therefore, of the indexes we evaluated, the EEG-BI appears to be the most accurate for quantifying midazolam-induced sedation during regional anesthesia.

In this study, α power increased as the OAA/S score decreased from 5 to 2, whereas β power decreased as the OAA/S score decreased from 4 to 1. It has been reported that benzodiazepine-induced sedation increases high-frequency β power.^{19,20} However, use of

Table 3. Calculated EEG_{50-VC} and EEG_{50-SH} Values for the 95% Spectral Edge Frequency (SEF) and Bispectral Index (BI)

	95% SEF	BI
EEG _{50-VC} *	17.8 ± 3.1	79.3 ± 8
CV (%)	17.3	10.2
EEG _{50-SH} †	16 ± 3.5	70.8 ± 14.3
CV (%)	21.9	19.8

CV = coefficient of variation [(SD \times 100)/mean value]

* EEG_{50-VC} for response to verbal command

† EEG_{50-SH} for response to shaking of the head

β power as an effect parameter requires constant verbal stimulation and a responsive subject. Greenblatt *et al.* found that the increased EEG β power band was lost when the subject slept, decreasing the usefulness of β power band for studying the effects of larger doses of midazolam.²¹ In a study involving dogs, Fleischer *et al.* demonstrated that the infusion of midazolam produced dose-related EEG changes with high-frequency α and β power changing to low-frequency δ and θ power.⁹ In our clinical study, we did not observe an increase in the δ or θ power after administration of 9.1 ± 4.3 mg intravenous midazolam (mean \pm SD). This apparent disparity in results could be due to species differences and to differing definitions of the power bands, variable settings for the frequency filters, and subtle low-frequency motion artifacts induced by eye movements. The EEG power bands, therefore, would not appear to be good indicators for assessing benzodiazepine-induced sedation.

The 95% SEF has been shown to predict hemodynamic responses to laryngoscopy and intubation.⁸ In the current study, a good correlation existed between 95% SEF and clinical responses at deeper sedation during onset phase (OAA/S scores from 4 to 1). These results confirm the preliminary findings of Billard *et al.* during intravenous anesthesia.²⁰ Buhner *et al.* demonstrated that the initial transient increase in 95% SEF correlated with the midazolam-induced power shift from α to β bands.²² However, with deeper sedation, the power increase in the δ band moved the 95% SEF toward lower frequencies.²² The coefficients of variation for both EEG_{50-VC} and EEG_{50-SH} were less with the 95% SEF compared to the power bands or MF. These data suggest that the 95% SEF is superior to the use of the EEG power

bands and MF in assessing midazolam-induced sedation. However, 95% SEF is a less accurate indicator of the degree of midazolam-induced sedation than the EEG-BI during both the onset and recovery phases.

When using sedative medication as part of a monitored anesthesia care technique, the anesthesiologist attempts to titrate the drug to optimize patient comfort while maintaining cardiorespiratory stability and intact protective reflexes. Based on the EEG-BI response curves, we recommend a EEG-BI value greater than 80 to achieve and maintain an OAA/S score of 3 or greater. Therefore, anesthesiologists may be able to improve the accuracy of titration of midazolam and other sedative-hypnotic drugs (e.g., propofol) during local and regional anesthesia by using the EEG bispectral monitor as an adjunct to their routine clinical assessment. The major limitations in using this EEG device to monitor sedation relate to the time required to place the monitor leads and the expense of the monitoring device. Future studies need to examine the relationship between OAA/S scores and EEG parameters with other centrally active sedative and analgesic drugs in the operating room and intensive care settings.

In conclusion, the EEG-BI appears to accurately predict the OAA/S score in patients receiving midazolam for sedation during regional anesthesia. Of the EEG variables evaluated in this study, the EEG-BI appeared to be the most accurate for assessing the depth of sedation.

The authors thank the postanesthesia care unit nurses and the residents in the Department of Anesthesiology and Pain Management, for their cooperation during this study. They also thank Nassib Chamoun, Paul Manberg, Ph.D., and Pat Embree, C.R.N.A., Aspect Medical Systems, Inc.

Appendix. Observer's Assessment of Alertness/Sedation (OAA/S) Scale²

Responsiveness	Speech	Facial Expression	Eyes	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	—	—	2
Does not respond to mild prodding or shaking	—	—	—	1 (asleep)

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